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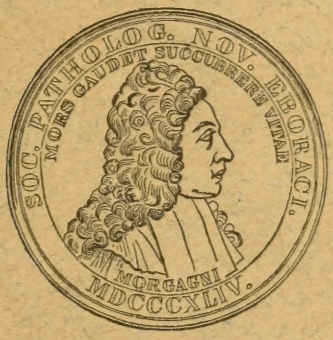
OF THE

NEW YORK PATHOLOGICAL SOCIETY



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Dr. Charles Norris, *President.*

URETERITIS CYSTICA CHRONICA.

(The clinical and autopsy records of a case with bilateral double ureters.)

BOND STOW, A.M., M.D.

The object of this short paper is to bring before you in a cursory review the conclusions reached on this subject by well-known authorities, and particularly to invite your consideration to some recent experimental work by Dr. R. Giani, of Turin, Italy, which throws considerable light on this much debated pathological problem.

The subject is one that has proven solely of pathological interest, although the writer sees no reason why under certain conditions a skilled cystoscopist should not detect this condition during life.

Morgagni,[1] Rayer[2] and Rokitansky[3] were the earliest writers to mention this affection, the latter describing the same in the following clear, concise manner.

"In the mucous membrane of the urinary tract, especially of either ureter, generally in large numbers and groups, there sometimes arise cysts varying in size from that of a grain of wheat to that of a pea, and others of microscopical dimensions. They contain a thin serous or thick colloid, clear or yellowish brown fluid, or gluey resinous clumps."

Virchow[4] maintained that these cysts are true retention cysts the same as the ordinary mucoid cysts of the vagina and are caused by a closure of the crypts of the mucous glands of the bladder and ureter.

Litten[5] was the first to give a careful microscopical study of these cysts and concluded without reservation that the inflammatory catarrh of the mucous membranes of the ureters led to a closure of its crypts and glands, retaining within their lumen their secretions, thus leading to a cystic formation.

Why these cysts occur so rarely in comparison to the great frequency of inflammation and catarrh of these mucous membranes he explains on the ground of the very wide openings of these crypts and the scarcity and uncertain distribution of the glands in these mucous membranes.

R. v. Limbeck[6] as early as 1887, gives an accurate description of this disease and its etiology as judged in the light of Giani's experiments, to be explained later on. He mentions two ways whereby these cysts take their origin:

First, through a union of folds of the proliferating mucous membrane, and second, by a budding process of its epithelium with later a central degeneration and liquefaction of these newly formed epithelial nests and sprouts.

That glands might possibly occur in these mucous

membranes and thus by closure of their exits become a source of these cysts he does not deny, but he states that he with many others has failed to find any such glands.

The English writers Silcock[7], Eve[8], Clarke[9], Bland-Sutton[10], have accurately described cases of this affection and have drawn particular attention to certain peculiar round or ovoid bodies that are constantly found within the cystic contents, which bodies they interpreted as forms of sporozoa.

Clarke claimed to have found bodies with large nuclei, a well marked network and a nucleolus; conditions only compatible with a perfect state of vitality of cell life. He believed there was an appearance as though the cell was in the process of mitosis although he failed to discover any mitotic figures. He thought it highly improbable that such bodies arose from degenerated epithelium and strongly maintained that they were some variety of protozoa and the direct cause of this disease.

Prof. G. Pisenti[11] describes a case of cystic-pyelonephritis, the right ureter containing numerous irregularly distributed cysts, and the left likewise, though fewer in number. The neck of the bladder also possessed numerous thickly placed small cysts whose contents were a clear fluid. In these various cysts he found the same bodies interpreted by the English writers as protozoa and he coincides with them as regards their etiological importance. He offers no proof that he ever discovered any signs of life in these bodies or that by experiment he was able to reproduce the disease through their agency. His conclusions are simply based upon microscopical observations whereby claiming not to have found within these cysts any transition forms of epithelium, he concludes that these peculiar bodies must be of parasitical and not cellular origin.

V. Kahlden[12] in an exhaustive monograph on this subject also concludes that in his case the histogenesis rests upon a parasitic basis although he does not definitely attempt to classify these supposed parasites, but simply states it as his belief, because of the great similarity between the bodies he found within these cysts and the myxosporidia (a psorosperm found in the bladders of fishes, particularly the pike), that therefore they are either a variety of this class of sporozoa or identical with them. He produces no evidence to support his conclusions from artificial cultivation of these parasites, neither from the reproduction of this disease through their agency by inoculation of lower animals.

One fact opposing the parasitic origin of this disease and prominently claiming our attention is, that no one as yet has found any of these protozoa in or among the epithelial cells of the mucous membrane of the genito-urinary tract or even the cells lining the walls of these cysts. They always appear in the colloidal mass within the cysts. It certainly seems reasonable to expect to find them occasionally (if only by accident) in or among the cellular epithelium when they are present in such large numbers and are supposed to be the causative factor in the formation of these cysts out of the epithelium of the mucous membrane of this tract.

A. v. Brunn's[13] studies on the normal mucous membrane of the genito-urinary tract have proven of great service in elucidating this problem, by showing the existence of certain epithelial bodies found beneath the superficial layer of cells of the mucous membrane, either disconnected therefrom or in direct continuance with the same. He claims that they are in no sense secretory glands as was formerly held by Virchow and Litten, since they fail to show a constant exit duct or central lumen

which is generally present in most glandular structures, and that there are never present within these cells any of those changes frequently observed in glandular organs while functionating. He believes these cellular accumulations are the result of a simple budding process of the normal mucous membrane due to an excessive stimulation and consequent proliferation of the surface epithelium. When these bodies are not disconnected from the surface he speaks of them as epithelial buds or sprouts and the others disconnected by an intervening layer of connective tissue as epithelial cell nests. It is from these cellular formations he maintains that the condition of cystitis and ureteritis cystica chronica arises.

Lubarsch[14] strongly contends against the parasitic origin of these cysts and agrees with v. Brunn, as he has observed all stages of degenerative transition of these epithelial cell nests from solid to complete cystic formations. Clear and forceful is the conclusion to be drawn therefrom, that this is the true origin of these cysts, the two things necessary being the presence of v. Brunn's cell nests and the continuous action of some injurious agent, the most frequent being inflammation arising from the existing calculi. The cysts arise by, first, a destruction of the centrally located cells out of which later is formed a colloid and granular detritus. Since this material finds no exit, by its increment the cyst increases in size until there is but a single layer of epithelial cells that bound the lumen of the ureter. He concludes from microscopical examination and the peculiar action of stains on these cell contents that the same is not a true secretion but simply a colloid mass originating from degenerated epithelium.

Lubarsch by no means thought that this was the sole method of origin of these cysts for at the close of

his article he really speaks of three ways: namely, those cysts that arise from the closure of mucous crypts as described by Virchow and Litten, those that come from a degeneration of v. Brunn's cell nests and those that are found at the trigone of the bladder due to misplaced prostatic glandular tissues.

Aschoff's[15] extensive studies on the mucous membrane of the genito-urinary tract would go to prove that in the newly born and those of early life no epithelial budding of the mucous membrane or cut off epithelial nests as described by v. Brunn and Lubarsch can be found in the genito-urinary tracts and even in adult life he found them to be very inconstant and chiefly confined to the upper third of the ureter.

Marckwald[16] found cystitis and ureteritis cystica in the newly born and claims, as does Aschoff, that an inflammation is not first necessary to originate these cell nests and cysts.

Stoerk[17], on the other hand, after a most painstaking and exhaustive study of this subject differs from v. Brunn in that he claims these cell buds and nests are secretory in nature as well as their contents and that it is by the retention of their secretions that a transformation of these glandular-like cell nests into cysts occurs.

He also differs from the views of Aschoff and Marckwald in that he strongly maintains that there must be first an inflammatory reaction to cause these cell nests even though traces of such a reaction may have entirely disappeared from present view. He draws attention to one very significant fact that certainly requires explanation, which is, that during extra uterine life nowhere in the body in any of the other mucous membranes can any analogy to v. Brunn's findings be discovered. What explanation can be offered that the

mucous membrane of the genito-urinary tract solely and frequently undergoes this proliferating budding process?

Finally I invite your attention to the most recent work done on this subject by Dr. R. Giani, of Turin, Italy. Giani[18] in a purely accidental way was surprised to find a condition simulating in every respect cystitis and ureteritis cystica chronica caused by some experiments he had instituted for a study of tuberculosis of the genito-urinary tract. He performed a suprapubic cystotomy upon rabbits and placed within the bladder some gelatin capsules containing a pure culture of tubercle bacilli. The external wound and bladder healed regularly. Free passage of urine occurred a few hours after the operation. In one case about 30 days later the capsule was passed through the urethra. In all the other cases the capsules became the seat of salty incrustations from the urine and were the centers of well formed and quite large calculi. The rabbits, twelve in all, were kept alive from fourteen days to three months. After fifteen days he discovered a chronic cystitis and scattered here and there in numerous places the mucous membrane showed marked tendency toward proliferation of its epithelial cells in more or less bud-like processes dipping down into the stratum propium. Later these became wholly separate from the mucous membrane. Still later he found degeneration and liquefaction taking place within their centers and thus the beginning of a small cyst. These epithelial sub-mucous nests varied very materially in size. Sometimes they remained throughout one solid mass of epithelial cells. Complete cystic formation rarely occurred before the 40th day from which time on they increased considerably in size and number. He universally found these cysts, in toto or in part, filled with a fine granular detritus composed of red blood

corpuscles, leucocytes, fragments of nuclei, and broken down epithelial cells. Besides these he frequently found in these cystic contents peculiar bodies whose form were generally round or elliptical averaging in size about 20 to 25 micra though sometimes they were as large as 40 and some were as small as 7 or 8. The protoplasm of these bodies possessed no particular structure. It was more or less coarsely granular and refractory against anilin dyes, having a hyalin, almost glossy appearance, coloring intensely with eosin. Sometimes they contained no nucleus, then again he found a body simulating a nucleus which stained deeply with hematein.

This description corresponds very closely to that of the so called parasites (protozoa) supposed to have been found in the cysts by certain English and Italian writers and claimed by them to be their cause. Such bodies were found only in the cysts and never free in the epithelium of the mucous membrane, neither in the solid cell nests above spoken of and out of which cysts eventually arose, nor in the cell accumulations on the surface of the mucous membrane.

In the light of these experimental findings it is not possible further to give credence to the parasitic origin of this affection. The chronic irritation due to the inflammation set up by the capsules that acted as foreign bodies seems an essential etiological factor.

Giani found the cysts greatest in number where the irritation would appear to have been the greatest.

Further experimentation by ablation of the mucous membrane of the bladder by a Volkmann sharp spoon produced similar results.

Giani also observed in the case of hypertrophy of the prostate where the middle lobe was removed by suprapubic cystotomy that the mucous membrane of the blad-

der over this lobe was covered by numerous epithelial indentations and epithelial nest formations in the submucosa, either isolated or in direct communication with the surface epithelium. These undoubtedly arose from chronic irritation of the mucous membrane of the bladder at this part due both to the hypertrophic middle lobe of the prostate and the daily repeated catheterizations which had taken place for the past three years.

In conclusion one question appears difficult to answer and I cannot help but believe that there is still a very important factor in the etiology of this disease that is yet to be explained.

Ureteritis cystica chronica is a very rare affection. Lubarsch in over 3000 autopsies met the condition but four times.

The writer's experience which certainly covers many hundreds of autopsies has met with the condition but once; the specimen being presented here to-night (see illustration). I find in the entire literature not over 50 cases reported.

If we are to believe that inflammatory irritations of mucous membrane of the genito-urinary tract set up a proliferation of its epithelial surface so that buds and cell nests are formed out of which later cysts are formed, then why, knowing as we do that inflammation of this tract is of very frequent occurrence, is cystitis and ureteritis cystica chronica so rarely met with? There are several cases reported in the literature of double ureter on one side in which this affection was found.

The specimen presented here to-night is one of bilateral double ureters in which there is complete cystic degeneration of all four ureters. So far as I have been able to glean from the literature it remains the only

specimen of its kind. The cystic degeneration in this case is confined to the ureters. Why?

Is the presence of ureteritis cystica in these cases of reduplication of the ureter purely a concomitant circumstance or has the congenital malformation some etiological significance?

I am not able to answer these seemingly pertinent questions.

Microscopical examination of many sections showed all the finding of the authors above reported especially the round and ovoid bodies in the cyst contents, the budding sprouts and cell nests in the mucous membrane of the ureters with degenerated cell and detritus material in their centers. Nothing was observed that would appear to enhance further the microscopical findings already reported, illustrations of which are plentiful in the literature herewith appended, nor to throw new light on the etiology of this much vexed problem.

Clinical History.

Anna Palil, 40, Hungarian, houseworker. Admitted to Metropolitan Hospital, New York, May 17th, 1906. Died, May 22nd, 1906, 9.25 A.M.

Family history negative. Does not use alcohol. Moderate tea and coffee drinker. No drug habits. Had usual diseases of childhood. Had an attack of articular rheumatism in adult life. No history of any venereal diseases. For the past three years has been complaining of her stomach. Refuses solid food. Says same causes her much distress. No history of any vomiting. No localized pain anywhere in body. Poorly nourished. Subcutaneous and muscular tissues wasted. Edema of both lower extremities. Abdomen presents a large ventral hernia. Face has a pained and distressed

appearance. Complexion is generally sallow with some cyanosis. Mucous membranes congested. No edema of face. Reflexes are all normal. Apex beat in sixth interspace and slightly to the left of the mid-clavicular line. Border of dullness to the right reaches the mid sternal line. Slight epigastic pulsation. A rough systolic murmur is heard at the apex, the same being transmitted to the left axilla. The second pulmonic sound is accentuated. The chest expansion is poor and appears slightly greater on the left side than the right. The apices are somewhat sunken. The interspaces are very much retracted and the ribs correspondingly prominent. Over the entire chest is heard a broncho-vesicular respiration except a small area anteriorly on the right side corresponding to about the location of the right middle lobe and the base of the left lung where no respiratory murmur is heard. Large inspiratory moist rales heard over the entire lungs. Expectorates a thick muco-purulent sputum. No tubercle bacilli. Examination of abdominal organs proved negative. Urinalysis showed: light amber color, 1.028 specific gravity, albumin, no sugar, and 1% of urea. Amount was 24 ounces in 24 hours.

Diagnosis: Mitral insufficiency with failing compensation, chronic bronchitis and edema of the lungs, chronic Bright's disease.

Autopsy: Autopsy began at 2 P.M., 4½ hours after death. Body very pale and anemic. Slight edema of both legs. Abdomen prominent due to gases. Pupils equally dilated 3 m.m. Post-mortem rigor slight, hypostatic congestion in dependent portions of body. No external marks on body. Peritoneum smooth, glistening and transparent. Peritoneal cavity contains about 500 c.c. of a clear pale amber colored fluid. Mesentery and

mesenteric glands show no change. Abdominal organs in normal positions. Diaphgram on right side at lower border of sixth rib and on the left side at seventh interspace. Anterior border of the lungs fully 5 cm. apart. Upper half of right pleural cavity is occluded by old tough fibrous adhesions; lower half filled with a clear pale amber colored fluid amounting to about 800 c.c. Marked thickening of pleura at base of right lung. Left pleural cavity partially occluded by old pleuritic adhesions, and contains about 1000 c.c. of a clear, pale, amber colored fluid. Pericardial sac contains about 200 c.c. of a pale clear amber colored fluid. Pericardium is smooth, glistening and transparent. Right ventricle is soft and collapsible; left is distended. Blood vessels on surface of heart are partially engorged. Heart muscle is of a light yellowish brown color, soft in consistency and readily torn. Left ventricle is distended and its walls measure 7 m.m. at the apex and 1½ c.m. at the base of the artic valve. Right ventricle is distended and its walls measure 2 to 3 m.m. Endocardium is smooth, glistening and transparent throughout. Pulmonary and aortic valves show no change. Tricuspid valve is widely dilated. Mitral valve shows recently formed vegetative growths along its free closing margin. The mitral valve is somewhat distended admitting the tips of three fingers. The heart weighs 483 grams. The upper lobe of right lung shows congestion and edema and from the bronchi exudes a creamy, greyish yellow, foamy secretion. The middle lobe is noticeably voluminous, firm to the touch, and its cut surface is of a greyish red color, smooth and glistening and solid and contains no air. The pleura over this lobe is thickened. The lower lobe shows hypostatic congestion and edema with chronic bronchitis.

The pleura covering the upper lobe of the left lung

is covered with numerous recent petechial hemorrhages. The upper lobe shows same as upper right lobe.

The lower lobe is covered by a thickened pleura. It is firm to the touch and upon its cut surface is smooth glistening and airless and of a dull greyish red color.

The larynx, trachea, and upper bronchi were filled with a creamy, foamy, greyish secretion and their walls were heavily congested. Nowhere throughout the lungs was any evidence of tuberculosis. The spleen was of a dark mahogany brown color, capsule slightly thickened, slightly smaller than normal, weighing 180 grams. Cut surface showed trabeculae and Malpighian bodies prominent; pulp firm.

The liver weighed 1447 grams. Firm in consistency with slightly granular surface. Mottled yellowish brown in color. Capsule unchanged. Edges slightly rounded. Cut surface showed same to be finely granular. Acini indistinct. Blood vessels congested.

The pancreas showed no particular change. The stomach walls were covered by a thick, tenacious, slimy mucous. Blood vessels heavily congested. Mucous membrane atrophic, otherwise no change.

The intestines, large and small, showed passive congestion. The adrenals were normal. The bladder contained a foul, stinking, greenish fluid. Its walls were intensely congested. The ureters and pelves of both kidneys likewise contained a foul stinking greenish yellow pus.

There is a reduplication of the ureter on both sides. Each of the four ureters arises from a separate pelvis of the kidney. The two ureters on each side remain entirely separate and distinct throughout (being divided by ordinary connective tissue) and unite in one common

exit at the usual normal ureteral opening at the trigone of the bladder. (See illustration).

Each of the four ureters is very thickly studded from origin to within 4 cm. of its entrance into the bladder by innummerable cysts varying in size from that of a millet seed to that of an ordinary pea.

These cysts are both individual and massed in groups. Some are transparent and contain a clear serous fluid. Others are of an opaque greyish yellow color containing a thick ropy colloid material. A few seem harder than the others and contain a gluey resinous-like hard substance.

The pelves of both kidneys contain likewise a few scattered similar cysts whereas the bladder is entirely free from cysts of any kind. The right kidney is very firm in consistence, of a dark mahogany brown color and weighs 62½ grams. It measures 8 x 5 x 3 cm. It is coarsely granular on its external surface and the same is studded with numerous small individual and grouped abscesses.

Its capsule is thickened and cannot be removed without adhering kidney tissue. The cut surface is granular. The cortex ranges from 1 to 3 m.m. The pelves are intensely congested and inflammed. The one pelvis is in direct communication with three large well defined abscess cavities that extend to within 1 m.m. of the external surface of the kidney.

The pyramids are greatly distorted or entirely replaced by tough connective tissue. The blood vessels are prominent and arterio-sclerotic. The left kidney weighed 93½ grams and measured 8½ x 4 x 3½ cm. Its color, consistence, and other characteristics are very similar to those of the right kidney. Within the kidney and in direct communication with the pelves of the

kidney are large well defined abscess cavities that contain a foul, stinking, greenish yellow pus.

Diagnosis: Chronic bronchitis, passive congestion and edema of the lungs. Unresolved pneumonia of the middle lobe of the right lung. Chronic pleurisy. Hypertrophy and advanced fatty degeneration of the heart muscle with acute endocarditis of the mitral valve. Muscular insufficiency of the mitral and tricuspid valves. Cyanotic induration of the spleen. Early stage of cirrhosis of the liver. Chronic atonic gastritis. Passive congestion of the intestines. Chronic cystitis. Ascending pyelo-nephritis with hydronephrosis and advanced arterio-sclerotic granular nephritis. Complete bilateral reduplication of both ureters. Extensive ureteritis cystica chronica of all four ureters.

Photograph of entire genito-urinary tract.

A. One of the two left ureters opened throughout and showing the numerous cysts.

I. Pelvis of the kidney from which ureter A arises. The ureter A can be followed throughout to its common exit (with its fellow B) into the bladder at C.

B. The other left ureter unopened. The probe at H is passing into this ureter from its own pelvis. The lower end of the probe being seen at C.

D. Common opening into the bladder of the two ureters on the right side.

E. and F. The two ureters on the right side opened throughout from the pelvis of the kidney to the bladder. The numerous cysts lining their walls are plainly seen.

M. The dividing wall of connective tissue between the two right ureters.

U. Fundus uteri.

P. Posterior wall of vagina.

K. Right half of bisected bladder.

L. Left half of bisected bladder.

O. O. Ovaries, right and left.

R. K. Right kidney.

L. K. Left kidney.

Photograph Showing Entire Genito-urinary Tract

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Discussion.

Dr. Charles Norris said that he had never before seen a case like this. He would like to ask Dr. Stow whether there were any evidences of tuberculosis found.

Dr. Stow said that no evidences of tuberculosis were present throughout the body.

A CASE OF ACROMEGALIA.

CHAS. NORRIS, M.D.

The pituitary tumor in the case of acromegaly which I am about to present is that of a patient, a German by birth, who entered Bellevue Hospital in December, 1902, in the service of Dr. Frank W. Jackson, and who died four years later (Jan. 1907), also in Dr. Jackson's service. I take this opportunity to acknowledge publicly my thanks to Dr. Jackson for his courtesy and kindness in permitting me to report upon the clinical history of the case.

The man was single, a driver by occupation, and, when admitted to the hospital, was 33 years old. He gave the following history:

Six months previously, he was told that his face and hands were growing larger. At this time he began to have dizzy spells. Things became black before his eyes at times. His memory also became poor. His feet became so much larger, according to his statement, that he had to buy larger shoes. At this time he went to St. Francis Hospital, where he remained until two months before admission to Bellevue.

After his discharge from this hospital, he said he was unable to work on account of frequent dizziness, and sharp, radiating headaches. His tongue became enlarged, and impaired his speech somewhat. He became clumsy with his hands, and his gait was a little uncertain. He complained of indefinite pains in his arms. No other important symptoms were elicited, his chief complaint being attacks of dizziness, and severe headaches.

Family and personal history were negative. He had

never been ill before, save for a slight attack of bronchitis nine months previous to admission.

On admission he was fairly well nourished, and rather anemic. Muscles flabby. Poor muscular power. Lips thick. Eyes prominent, lids heavy. Nose large and prominent. Lower jaw projected slightly, although teeth met. Eyes reacted normally to light, and accommodation. Tongue somewhat enlarged, moist and tremulous.

Thyroid gland normal to palpation, and apparently not enlarged. Pulse was rapid, 110.

Heart. Normal, no murmurs.

Lungs. Normal.

Abdominal examination negative.

Hands showed general enlargement, involving bones and soft tissues. Nails were normal. Feet were enlarged, principally the great toes. Reflexes remarkably diminished. Blood examination showed a hypoleucocytosis, 3,400, and rather marked secondary anemia. Hemoglobin 60%. Urine was clear, acid, and contained no albumin, sugar or casts.

From the time of his admission, patient complained of dimness of vision, and severe frontal headaches. Two weeks after admission, opthalmoscopic examination was made by Dr. Reese, who reported: "Receding choked disc of both eyes. Veins and arteries very tortuous. Nerve margins blurred. Left nerve is atrophic, while right nerve shows beginning atrophy. Pupils react to light directly and consensually".

In January, 1903, without premonition, he was taken suddenly with an epileptic convulsion, lasting five minutes. General muscular spasms, with cyanosis, frothing at the mouth, and dilated pupils. The attack was followed by prolonged stupor. No recollection of

convulsions upon regaining consciousness. Six months later, he had a second convulsion, and from this time until his death, they recurred, gradually, and at decreasing intervals, toward the end, several times a week, and on some days, several convulsive attacks occurred. They were never preceded by definite aurae, nor were there at any time localized spasms which might point to a focal lesion. It may be said, however, that the attacks were usually preceded by more intense headache than usual. The headaches, usually frontal, were a persistent and distressing symptom, present the greater part of the time, and but partially relieved by drugs. The visual disturbance was progressive. During the last few months amaurosis was complete in both eyes. On May 19, 1903, in other words, about one year from the onset of the first symptoms, there was noted "neuritic atrophy of the left optic nerve, with no vision. Right eye has 20–20, with + 2.5 diopters spherical. Both nerve heads are filled with cicatricial tissue, margins much blurred. Field in right eye for form is normal, but for red, concentrically contracted".

There was a distinct deterioration of the mental faculities, evidenced by progressive loss of memory for recent events, and by fits of irritability. Other evidence of psychic impairment was never observed.

The nutrition of the patient was well preserved, and the weight remained approximately constant, 194 to 206 pounds. Digestion and appetite were excellent. No attacks of vomiting of the cerebral type were ever present.

Urine.—From his admisson in 1902, until May 1905, in other words, for the first three years of his disease, the usual clinical examination showed no abnormalities, save the occasional presence of a few hyalin casts.

From this date, in all subsequent examinations, glucose was present in amounts varying from a trace to 224 grams in 24 hours. The specific gravity ranged from 1.028 to 1.034, averaging about 1.034. Total twenty-four hour amount never exceeded four litres. No examination for acetone or diacetic acid is recorded. For a time in the Fall of 1903, and the Spring of 1904, the patient received Parke Davis's pituitary extract, without obvious benefit, although the patient said that he felt better.

During life, the patient had a marked stooping carriage. Death occurred on January 19. Patient had had a series of severe convulsions, followed by a coma and Cheyne-Stokes respiration.

Summary of Clinical History.—Total duration of illness, June, 1902, to January, 1907, — 4½ years.

Principal Symptoms: Progressive enlargement of jaw, nose, ears, hands and feet. Persistent frontal headaches, and attacks of vertigo. Gradually increasing loss of vision, ending in double optic nerve atrophy and practically complete blindness. Recurrent epileptiform attacks. Glycosuria for twenty-two months.

For the present purpose, only the significant features of the post-mortem findings need be given.

The body was that of a large, well-developed and well-nourished male, about 90.9 kilos in weight. Length of body on table, 5 ft. 8¼ inches.

The general appearance of the face was not as striking as it was during life; the lower jaw did not appear as large and prominent. The nose, however, was large and long. Lips were somewhat thickened. Teeth and gums were normal. The ears were markedly hypertrophied and symmetrical. This difference in appearance at autopsy was due, it seems to me, to the characteristic posture of the patient during life, his lower

jaw thrown forward, his head lowered, and marked stooping carriage. In other words, the kyphosis that was so prominent a feature in life was a physiological one, since the vertebral column at autopsy was found perfectly straight. Although the forehead was receding, the supraorbital ridges were only slightly prominent. The skull was brachiocephalic, 22½ inches, "sub-occipto-bregmatic". The eyes protruded markedly, even at autopsy. Chest was long and broad, the lower opening being especially wide. The sternum was not enlarged. The costal cartilages were broad, the fourth left, in its broadest portion, being 25 mm., in its narrowest, 20 mm. The ribs, although at autopsy they appeared to be broad and heavy, may be said to be only slightly larger than normal, corresponding in size to those of a man of the patient's size.

Circumference of chest, 38¾ inches. From tip to tip of acromion process, 18 inches. Glove measurement, 8½ inches. Across fingers, 8 inches. Middle finger, 4½ inches long. Foot measurement around metacarpal joint, 9½ inches. Circumference of big toe, 4 inches. From these measurements, it can be readily seen that the feet and hands were not greatly enlarged. Neither were the subcutaneous tissue and skin hypertrophied. Enlargement of both big toes, however, was a striking feature. No osteophytes were felt.

The small toes were likewise greatly enlarged. The fingers were large and sausage shaped. The nails were broad, but otherwise normal. The subcutaneous tissues of the toes and fingers were hypertrophied. The corium taken from the abdominal wall was hypertrophied.

To be brief, it may be said that the viscera were practically normal, with the exceptions to be noted. Considering the size of the body, it may be safely

asserted that the so-called condition of splanchnomegalia was not present.

Heart. Normal. Weighed 473 grams — normal to the body weight.

Liver. Weighed 2,930 grams, being slightly below weight in proportion to that of the body.

Spleen. Weighed 510 grams, being almost double in weight. The capsule was wrinkled.

Kidneys. Together weighed 360 grams. Normal relation to body weight.

Pancreas. Length 20 cm.; large; weighed 170 grams, in relation to the body weight ⅙ above normal. The organ was firm, the lobulations being distinct. No macroscopic lesions were noted. The organ underwent rapid post-mortem softening.

Thymus was persistent, and extended to the auriculoventricular junction below, and to the thyroid gland above. The left lobe was somewhat larger than the right, and very broad. Weight of gland was 70 grams.

Tongue. Was very large and broad, measuring from apex of tongue to apex of circumvallate papillae, 11 cm. Maximum breadth, 7 cm. The papillae were extremely large.

Lingual tonsils were large. In the pyriform fossae of the larynx, on the anterior surface of the epiglottis, numerous small, raised, grayish bodies, averaging 4 to 5 mm. in diameter, were present.

Thyroid. Thyroid cartilages showed reddish bone-marrow. Thyroid gland was symmetrical, normal in size and appearance. The cervical lymph nodes were somewhat increased in size, and slightly yellowish in color. The lymph nodes of other regions were normal in size. The only lymphatic hyperplasia that was noted was

found in the larynx and pharynx, the splenic follicles of the spleen not being hyperplastic.

Gastrointestinal Tract. Stomach, moderate *état mamelonné* in pyloric region. Otherwise the gastrointestinal tract was normal.

The genitourinary tract was normal, the penis and testicles being well developed.

The Cranium may be said to have been normal to the size of the body. The bones of the face, with the exception of the inferior maxillae, were not enlarged. The scalp tissues were normal. On stripping the scalp from the calvarium, the parietal bones were found markedly hyperemic. Bones of the skull were soft, being readily sawn. The temporal bones were thin, only 2 to 3 mm. in thickness.

Over the right frontal base, the bone measured 9.5 mm. Here the diploe was extremely hyperemic, 4 mm. in thickness. Outer table measures 3 mm, inner table 2 mm. Dura presents over both cerebral convexities, a number of flat, whitish chalky plaques, the largest 5 to 6 mm. in length. The pia shows no opacities. The cerebral convolutions over the convexities are markedly flattened, the sulci being almost obliterated.

On lifting the frontal lobes, a tumor mass was found on the inferior surface of the right frontal lobe. Owing to the apparent attachment of the tumor to the pituitary gland, the brain was removed with sella turcica, and adjacent parts of the base of the brain. The tumor mass need not be described, except to mention the measurements. The tumor mass seen in the frontal lobe measured 5 cm. in length antero-posteriorly, 4.5 cm. in breadth, and approximately 3 cm. depth. It was dull grayish, approximating brain tissue in color and consistency. On section it had a fleshy appearance, and was in places hemorrhagic.

The tumor mass was connected by a broad pedicle to the pituitary gland proper, which was enlarged, being represented by a spheroidal mass of tissue, roughly speaking, 30 mm. in diameter. The bone of the sella turcica was very thin and fragile, and was readily separated from the pituitary gland tumor proper, with forceps. The adjacent sphenoid cells were likewise distinctly atrophied, and filled with a semigelatinous fluid.

The pituitary tumor, in its growth, has enlarged the sella turcica, and pushed aside the sphenoid cells and the clinoid processes. The tumor has advanced upward and forward, pushed aside the right olfactory lobe in front of it, and has gradually developed into the large tumor which was found at autopsy. In its growth, it has invaginated the R. lateral ventricle, especially its anterior horn, the ventricle being converted into a narrow slit, and the corpus striatum, with the internal capsule, compressed into a narrow band, which, in its widest portion, is approximately 1 cm. in breadth. The sections and photographs show the distention of the left lateral ventricle.

The brain with the pia mater was above the normal weight, 1,678 grams. The medulla and spinal cord were broad and large. There are two calcareous plaques, similar to those found in the dura mater of the cerebrum, in the spinal pia mater.

Osseous System.—The marrow of the ribs is extremely scanty. Marrow of one of the lumbar vertebræ may be said to be normal in appearance. Marrow of the lower end of the femur was, to the best of my recollection, normal in appearance.

In review, the main features of the necropsy are the following:

Enlargement of the inferior maxillae, of the nose

and the ears, characteristic of those found in acromegaly. Likewise enlargement of the fingers and toes, especially the great toes. The presence of a large pituitary tumor. Hypertrophied tongue. Hyperplasia of the lingual and pharyngeal lymphadenoid tissue. Persistent thymus. Large pancreas. Large spleen. Hypertrophy of the corium of the abominal wall.

Microscopic Examination.— Examinations of the sections from the liver, spleen, heart, kidneys, suprarenals, small and large intestines, show no noteworthy features.

Testicles. — Show active spermatogenesis.

Thyroid Gland.— Sections of the thyroid gland; the alveoli present the normal variations in size invariably observed in all normal thyroids. No colloid vesicles were noted in the sections or in the gross.

Sections taken from various parts of the tumor resemble closely the normal histological structure of the pre-hypophysis. The tumor is made up of a mass of spheroidal or oval cells, which are grouped in irregularly-shaped lobules or alveoli, by delicate capillary walls, apparently composed only of endothelial lining. At the periphery of the lobules, the cells appear to lie directly upon the endothelial lining of the capillaries. In sections stained by Van Gieson's stain, dilated connective tissue fibrils are, however, made out, separating the cells from the capillary wall. The tumor is everywhere very vascular, and in a few places small areas of hemorrhagic infiltration are present. The lobules are in the main closely packed with cuboidal cells. The nuclei are small, usually oval. The chromatin network is scanty, nuclear membrane is distinct. The protoplasm is moderately eosinophilic, and the cell boundaries indistinct. The

stroma, as above said, is scanty. Nowhere in the tumor have whorls of connective tissue been seen.

The two types of cells described in the normal prehypophysis cannot be made out, or their presence is only in a few places suggested. It is, however, quite true that there are variations in the staining reactions of the cells, but these are insignificant, in some places the protoplasm being more eosinophilic than in others. In some places, the protoplasm of the cells appears more granular and the lumina of the acini contain globules of various sizes, as well as a smaller number of free cells, some of which are well preserved, while others have poorly staining nuclei. In many sections there are seen groups of larger and smaller acini, lined with a single layer of high columnar epithelium, the cells of which are closely packed together. The nuclei of these cells are oval, and have a scanty chromatin network and small nucleoli. The protoplasm of these cells is granular and moderately eosinophilic. In their lumina, is found more or less granular material, and globules staining with eosin. These globules invariably stain less intensely than the red blood cells.

The most striking feature of the tumor may be said to be its extremely cellular and vascular structure. The abundance of the material and globules present in the lumina of the acini is a most noteworthy feature, and in this respect, the tumor may be said to vary from the normal anterior lobe of the pituitary gland.

The histological descriptions of the adenomatous tumors of the pituitary gland in cases of acromegaly, do not mention such a condition, as far as I recollect, but I am not yet sufficiently familiar with the literature of the numerous articles to be sure of my ground. Frozen sections stained with Scharlach Roth present a few fat droplets, much less than in the normal gland.

Thymus.—Microscopically, shows the structure usually found in the organ which persists during adult life.

Pancreas.—Except for the changes to be described in the islands of Langerhans, is normal. There is no interlobular or interacinal pancreatitis. There are small areas of post-mortem degeneration, which present the usual features: that is, the nuclei stain poorly or not at, all, and the tissue takes with hematoxylin a diffuse bluish tint. The vessels in places show slight thickening. The islands in the sections taken from the middle regions of the organ, show the following changes: The cells of many of the islands are hyperplastic, and here vascularity of the capillaries is a noteworthy feature. The cells frequently take on a rather intense eosinophilic stain. In a few islands, the changes noted by Opie are marked; that is, the islands are composed mainly of an indefinite substance, which has undergone hyaline degeneration. The lesion of the islands may be considered as an early stage of the condition which Opie has described in the pancreas of cases of diabetes mellitus.

On account of the lack of time at our disposal, it will be impossible to give a description of the lesions and various theories which have been formulated upon the etiology of acromegalia. Since Sternberg's elaborate article in Nothnagel's System, which appeared in 1897, little advance may be said to have been made in our knowledge of this disease.

Sternberg reviewed 210 cases. Since that time, numerous other cases have been reported. Tamburini, in 1897, reported upon 30 cases with autopsies. He noted that all had tumors of the pituitary—either a simple hypertrophy of the gland, or a total involvement in an adenoma, in which were preserved the principal elements of the gland. Tamburini was the first to bring out the

theory of hypersecretion as the etiological factor of the disease. He based his view on the following facts:

In acromegalia, the gland was never atrophied, and the symptoms of the disease were absent in cases of pituitary tumors which are heterological or atypical of the normal pre-hypophysis, in other words, where the gland was atrophied or diseased, or in a condition where it was reasonable to suppose that abolition of its function has occurred, the disease was not present. He therefore concluded that the constant presence of a tumor, and the nature of these tumors—hypertrophy or typical adenoma—supported the view that acromegalia is caused by a hypersecretion of the gland. The disease process is thus analogous to that of Basedow's disease.

In an elaborate and complete article which appeared in 1898, in which three cases, with autopsies, were reported, Brooks has supported Tamburini's hypersecretion theory.

Sternberg has divided cases of acromegalia into three groups, according to the duration of the disease. (1) The benign form, the disease running a slow course (50 years) with slight symptoms. (2) The usual form, 10 to 20 years. The majority of cases fall in this group. (3) The acute malignant form, 3 to 4 years. The cases now reported would fall in this group.

Six cases were reported by Sternberg, as belonging to the acute group. One of these was by Hansemann. In all the cases running an acute course, and only in these, was there observed a true sarcoma of the gland. These are of great interest in connection with the etiological relationship of a hypersecretion of the gland to the disease process. For, in a true sarcoma of any organ, one would not expect to find hypersecretion. Brooks, in order to overcome this difficulty, has boldly asserted that

the cases reported as sarcoma were not correctly diagnosed, claiming that they were probably all of them adenoma or hyperplasia. It seems almost impossible to believe that this view can be correct, for it is reasonable to suppose that such an observer as Hansemann would be familiar with the normal structure of the pituitary gland.

In the case now reported, the resemblance of the tumor of the normal gland is so very striking that I believe no one could fail to identify it as the pituitary gland.

The point I wish to emphasize especially this evening, is my firm conviction that in doubtful cases of acromegalia, the so-called formes frustes, that is, those cases in which the upper jaw is large, the lower being small, the face presenting the *type carré*, as opposed to the *type ovoide*, the diagnosis of the disease cannot be made from the histological appearance for the following reasons: First, because it is extremely difficult to be certain of the existence of hypertrophy in any gland, especially so in the case of the pituitary gland, and, second, because the presence of a small adenoma is not an unusual occurrence where no acromegalia is present. Erdheim thus reports a case of a man 42 years old, with an adenoma, the gland being normal in size. We have the same condition of affairs in connection with the thyroid, for it is undoubtedly true that many cases of parenchymatous struma are not accompanied by Basedow's disease.

In many cases of acromegalia, the gland has been found normal in size, and special emphasis seems to have been made upon the soft condition of the organ, a not unusual characteristic in cases dying with high fever, in meningitis, etc., where the post-mortem changes may be rapid, and also where care is not exercised in removing the gland from its bony surroundings.

Special attention has been called to the increased number of chromophile cells in the pituitary tumor of acromegalia. These cells are considered to be the functionating cells of the gland, and this fact has lent support to the hypersecretion theory. In our case, the chromophile cells are not increased in number, and, in fact, none of the cells can be said to resemble the chromophile cells which are found in normal glands, a statement in accord with Erdheim's description of the histological structure of the pituitary tumor in the case of acromegalia he reported.

Before closing, it may be of interest to state briefly that gigantism is frequently associated with acromegalia. According to Sternberg, 20% of the acromegalics are over 177 cm. in height, that is, 5 ft. 11 in., and 40% of all giants are acromegalics. It is thus seen that all giants are more often acromegalics than acromegalics are giants. According to Kundrat, giants are subject to all sorts of dystrophies and vegetative disturbances, and therefore, they are predisposed to become acromegalics.

The association of glycosuria with acromegalia is a very constant one. The physiological relation of the gland to the pancreas, has, as far as my knowledge extends, not been definitely settled. That the relationship between the pituitary and the thyroid gland is a close one, is well known. A persistent thymus has been noted in a large number of cases.

Two views are held concerning the two types of cells found in the gland. (1) Saint Rémy (1892) suggested that the two types of cells were merely functional stages of one cell. Benda (1900) was apparently able to trace the transition from the chromophobe or chief cell to the eosinophilic or chromophile cell. The small cells, with few granules, according to him, are the indefinite em-

bryonal cells which are multiplying, the large granular cells being actively functionating.

Scaffidi (1904) held the opposite view, namely, that the two types of cells have different functions, each type of cell producing a specific substance, a view apparently confirmed by the experimental results obtained by Schäfer and Vincent (1899) who extracted two substances from the gland, one depressing, the other stimulating the nervous system, and raising the blood pressure.

Benda.—*Berl. klin. Wochenschrift, 1900, XXXVII, pp. 1205–1210.*

Brooks, Harlow.—*Acromegalia. Archives of Neur. and Psychopath, 1898, I. p. 485.*

Erdheim.—*Beiträge zur path. Anat. und allge. Pathol., 1903, Bd. 33, p. 227.*

Saint Rémy.—*Arch. de Biologie, 1892, XII, pp. 425.*

Scaffidi.—*Arch. für mikr. Anat., Bonn, 1904, LXIV, p. 235.*

Schäfer and Vincent.—*Journ. Physiol, 1899, XXV, p. 87.*

Sternberg.—*Nothnagel's System, 1897.*

Tamburini.—*Archiv. de Neurologie 1897, Tome V. p. 621.*

Discussion.

Dr. J. H. Larkin asked Dr. Norris whether he had made any observations on the condition of the bone in connection with the sella turcica. The tumor might have arisen from the stalk of the gland and not from the gland primarily. This would bring out a very interesting condition of affairs, and it would be interesting to know whether the bone in connection with the gland was necrotic or had been eroded.

Dr. Harlow Brooks said that since Dr. Norris had been kind enough to refer to his paper he would like

to say a few words in defense of his attitude. In addition to the three cases which he had reported he had had three other autopsies since. In all of these he had found conditions identical with his first three cases. All of them were younger cases. One of the original cases reported he had considered as of great value because the patient had died of a concurrent infection in the early stage of the disease. In this case an adenoma of the hypophysis had been found in which the new formed cells were entirely of the chromophilic type. Dr. Brooks had then advanced the theory that the condition was due to a hypersecretion of the gland elaborated by the acidophilic cells alone. In regard to his position as to what he considered the faulty diagnosis of sarcoma by Hansemann, Virchow, and others, Dr. Brooks said that in none of these cases were there any metastases. In most of the cases the duration was not less than ten years, in all from four to ten years. Did it not seem rather strange that we could have here a sarcoma situated in such an advantageous position, running for ten years without a single metastasis? He thought a careful analysis of these cases would lead one to see that he had not been so far wrong in thinking that a mistake might have been made in diagnosis. Another thing which seemed to him of importance in regard to the sarcoma theory was that in none of the cases had there been any actual infiltration of the tissues from the tumor growth. In the cases described, while the sella turcica had undergone necrosis, in none were the tumor cells described as infiltrating the bone. Dr. Brooks still thought that no sarcoma had been proved to be present in a case of acromegalia. Of course, sarcoma of the hypophysis had been described, but it would be recalled that it was very hard to get a sarcoma of the hypophysis. If there is a sarcoma it

must arise from the mesodermal elements which are infrequent in the prehypophysis and which usually simulate the normal cells of the epiderm or at least of the entodermal cells. Dr. Brooks had seen one case which had somewhat shaken his theory. This was a case of adenoma of the hypophysis of sufficient size to make a diagnosis possible. The cells in this case were of the same variety before mentioned, but nevertheless acromegalia could not be demonstrated. This had shaken his theory more than anything else.

Dr. Norris said, in regard to Dr. Larkin's question, that in endeavoring to make his paper as short as possible he had omitted some points. The brain had been removed with the sella turcica and adjacent bones. The sella turcica was converted into a delicate shell of bone. He was sorry that he had given a wrong impression in speaking of the cases described as sarcoma; in fact, he was inclined to think that Dr. Brooks was perhaps right in saying that a mistake in diagnosis had been made, though it was hardly possible to conceive that such observers could make a diagnosis and not know what a normal gland looked like. In his own case he thought that it would be impossible to make a mistake in diagnosis.

THE PHENOMENA OF AGGLUTINATION FROM THE STANDPOINT OF COLLOIDAL CHEMISTRY.

CYRUS W. FIELD, M.D.

I wish to bring to your attention this evening the result of some work which has been going forward for the last six or seven years in colloidal chemistry, especi-

ally as this work bears on the phenomena of agglutination and precipitin reactions.

Linder and Picton, in England, determined the coagulative effect of various salts on colloidal arsenic sulphide, and found that this power was a function of the metallic cation and varied directly as its valence. (That is, if one part of a monovalent ion will flock out of solution one part of a colloid, one part of a divalent ion will flock out 35 parts of colloid, and one part of a trivalent ion will flock out 1,023 parts of colloid. This, as you will see, is in the ratio of $1 : x : x^2$, or in geometrical progression. If we represent x by an arbitrary number, 32, we then have 1 : 32 : 1,024. This is in very close agreement with the figures obtained by actual experiment.)

Hardy, working with coagulated egg albumin, found the same phenomena and explained it on the same basis. Billitzer and Bechhold have both worked on this subject with various colloids and also with suspensions, such as lamp black and bacteria. They found the same action; that is, they found that these colloids and suspensions were flocked out of solution by the electrolytes.

Buxton, Shaffer and Teague published a paper last summer in which they demonstrated two things; first, that it required less electrolyte to flock out bacteria which had been saturated with their specific agglutinin; second, that bacteria to which an insufficient amount of electrolyte to cause flocking out had been added, still traveled to the anode, and that when more than enough electrolyte than was sufficient to cause flocking was added, there was a reversal of the sign of the bacteria; that is, they traveled to the cathode.

When dialyzed bacteria are brought into the presence of their dialyzed specific agglutinins they ab-

sorb the agglutinin, but the organisms are not flocked out. If they are washed with distilled water and thus separated from all traces of their serum, and then suspended in distilled water, we have a preparation to which we apply the term agglutinin bacteria.

Table I shows the irregular series of agglutination; for instance, the colloidal platinum is flocked out at 2 normal to a 1–20 normal concentration of the salt. From 1–50 normal to a 1–1000 normal, no agglutination takes place; but at a 1–1500 normal to a 1–4000 normal we again have agglutination.

The dialyzed typhoid bacilli are flocked out from 1–10 normal to a 1–1000 normal. In this series we see a very pretty prozone; that is, no flocking has taken place in concentrations above a 1–10 normal. But in the case of the agglutinin bacilli, there are traces of agglutination from a 2 normal to a 1–20 normal, and complete agglutination at a 1–50 normal; then we have no agglutination taking place until we reach the 1–4000 normal and 1–6000 normal concentrations. Here we have a prozone from a 1–200 normal to a 1–2000 normal concentration of the salt.

The theory in regard to this is that all colloids carry an electric charge. For instance, bacteria are electronegative. Colloidal silver, gold, platinum, etc., are also electronegative. Aluminium hydroxid, ferric hydrate, and a number of other colloids are positively charged. Now, Bredig has shown that the surface tension of mercury when in contact with an electrolytic solution is greatest when the potential is least; in other words, when the electric charge is decreased, the surface tension is increased. We see, therefore, that when the charge of these particles is lowered the surface tension is increased and they must in some way overcome this tension. To

TABLE I.

Abstracted from Buxton and Teague.

Concentration of Fe_2Cl_6	Colloidal Platinum	Typhoid Bacilli	Agglutinin Typhoid Bacilli
2 Normal	+ + +	0	Trace
1 Normal	+ + +	0	Trace
1–2 Normal	+ + +	0	Trace
1–4 Normal	+ + +	0	Trace
1–10 Normal	+ + +	+	Trace
1–20 Normal	+ + +	+ +	Trace
1–50 Normal	0	+ + +	+ + +
1–100 Normal	0	+ + +	Trace
1–200 Normal	0	+ + +	0
1–400 Normal	0	+ + +	0
1–600 Normal	0	+ + +	0
1–1000 Normal	0	+ +	0
1–1500 Normal	+ + +	0	0
1–2000 Normal	+ + +	0	0
1–4000 Normal	+ + +	0	+ + +
1–6000 Normal	0	0	+ + +
1–8000 Normal	0	0	Trace
1–16000 Normal	0	0	0

do this they unite to form a less number of particles of larger size, because the total surface of two equal spheres is more than that of one sphere of double the mass of one of the smaller spheres. It is believed that these negatively charged colloids adsorb the positively charged metallic ions and in this way their charge is lowered and their surface tension is increased.

If this be true, the colloid particles should travel more slowly; that is, if they coalesce and form particles of a larger size, it should take a greater current to move them.

This point has been worked out by Burton, under J. J. Thompson in the Cavendish Laboratory. He used colloidal gold and silver, and flocked them with aluminium sulphate.

TABLE II.

Abstracted from BURTON.

Grams of Al	Specific Conductivity	Pole to which particles traveled	Velocity cm. per sec.	Precipitation
		Silver Solution		
0	$31.\times10^{-6}$	+	22.4×10^{-5}	0
$14.\times10^{-6}$	30.3×10^{-6}	+	7.2×10^{-5}	+ + +
$30.\times10^{-6}$	29.7×10^{-6}	—	5.9×10^{-5}	Trace
$77.\times10^{-6}$	28.5×10^{-6}	—	13.8×10^{-5}	0
		Gold Solution		
0	3.6×10^{-6}	+	$33.\times10^{-5}$	0
$19.\times10^{-6}$	5.2×10^{6}	+	17.1×10^{5}	— — —
$38.\times10^{-6}$	6.6×10^{-6}	—	1.7×10^{-5}	+ — +
$63.\times10^{-6}$	11.6×10^{-6}	—	13.5×10^{-5}	0

In Table II it is seen that the colloidal silver travels to the anode at a velocity of 22.4×10^{-5} when no aluminium is present; but when 0.000014 grams of this cation are added, the particles move at a velocity of 7.2×10^{-5}, or only one-third of the original rate. When 0.00003 grams of aluminium are added, the direction in which they travel is changed; that is, they now pass to the cathode; and the velocity is 5.9×10^{-5}.

The column under precipitation shows at what points they are agglutinated. I need not discuss in this place the significance of the other figures.

Table III shows the rate at which typhoid bacilli travel after having been treated with varying amounts of Fe_2Cl_6.

As will be noted, when no salt was present they wandered 2 cm. toward the anode in 60 minutes; but when they had been treated with a 1–6000 normal Fe_2Cl_6 solution, they required 110 minutes to travel 2 cm. in the same direction. When a 1–100 normal solution was added, they did not travel at all as they were completely agglutinated. If a 1 normal solution was added they moved to the cathode 2 cm. in 150 minutes; and when a 5 normal solution was added they traveled the 2 cm. in 115 minutes.

TABLE III.

Concentration of Fe_2Cl_6	Sign of Charge	Wandered 2 cm, in	Agglutination
0	—	60 min.	0
1–6000 Normal	—	110 min.	0
1–100 Normal	?	∞	+ + +
1 Normal	+	150 min.	Trace
5 Normal	+	115 min.	Trace

As is seen the sign is changed when they are treated with either a 1 normal or a 5 normal Fe_2Cl_6 solution.

It has been shown that bacteria when heated give up their agglutinins. That this same thing occurs with electrolytes that have been adsorbed is shown by the increased conductivity after heating to 50° C. for 1 hour, as may been seen in Table IV.

TABLE IV.

10 c.c. typhoid bacilli—40 c.c. of 1-80 normal $CuCl_2$ sol. 18° C.

Treatment	Ohms	Mohs
The above 50 c.c. at once	16,667	57.2×10^{-6}
The above 50 c.c. 24 hrs. later	14,667	$68. \times 10^{-6}$
Bacteria thrown down by centrifuge and A. & B. tested A 15 c.c. of sediment—28.5 c.c. of H_2O	122,223	8.18×10^{-6}
B 2 c c. of supernatant fluid—28 c.c. H_2O	220,000	4.5×10^{-6}
A heated to 50° C. for 1 hr.	84,614	10.5×10^{-6}
B heated to 50° C. for 1 hr.	220,000	4.5×10^{-6}
A centrifuged and sediment dil. with 15 c.c. H_2O	366,667	2.7×10^{-6}
Heated to 50° C. for 1 hr.	275,000	3.6×10^{-6}

There is a point which this theory explains, in regard to agglutination, and that is the prozone. For we believe that in this zone the charge of bacteria or colloidal particles has passed the isoelectric point, and that they are now charged with the opposite sign; therefore, the surface tension is reduced sufficiently to permit them to remain in suspension or in colloidal solution. This explanation seems to me to be much more rational than that advanced by Eisenberg who following Ehrlich's hypothesis explains this by suggesting that there is a substance in the serum which has a greater affinity for

the bacteria than the agglutinins; but that this has no agglutinating action; and that in this way this substance blocks the receptors of the bacilli and so prevents them from uniting with the agglutinins.

This same theory (the neutralization of the electric charge) has a bearing on immunity. For instance, Noguchi has shown that if an acid is added to a complementary serum the complementary action is destroyed; on the addition of an alkali the action reappears when the neutral point is reached, but again disappears on the addition of more alkali. The explanation appears very simple when we know that the surface tension between the colloidal particles and the serum is increased on the addition of acid and the size of the particles is increased. Owing to this enlargement the complement is bound by these larger colloidal particles and so can not act; but on the addition of an alkali the surface tension is decreased and the particles again separate and the complement is set free. When serum is heated to 55° C., the size of the particles begins to increase, and when the serum stands for a time the state of aggregation of the colloidal particles increases. In view of this it seems to me that inactivation of complement is a physical phenomena and not a chemical action, that is, it is entangled in the larger colloidal aggregate.

The question now arises, how do colloids of the same sign act? Agglutinins carry a positive charge and bacteria a negative charge; and it is easy to understand this phenomena. But toxins and antitoxins are both positively charged colloids. Personally I have no doubt that two colloids of the same sign can unite. I have recently prepared an extremely pure ricin and by immunizing rabbits to this have got an antiricin. The ricin is positively charged, and tests of the antiricin produced in

these rabbits have shown that it also is a positively charged colloid. I do not think that the two colloids unite chemically, but that they do adsorb one another and perhaps ultimately a solid solution is formed. I am working on this point and hope to be able to determine something in regard to it soon.